SPECIAL VIRUS CANCER PROGRAM

Research Logic for the Special Virus Cancer Program

Viral Oncology, Division of Cancer Cause and Prevention, NCI
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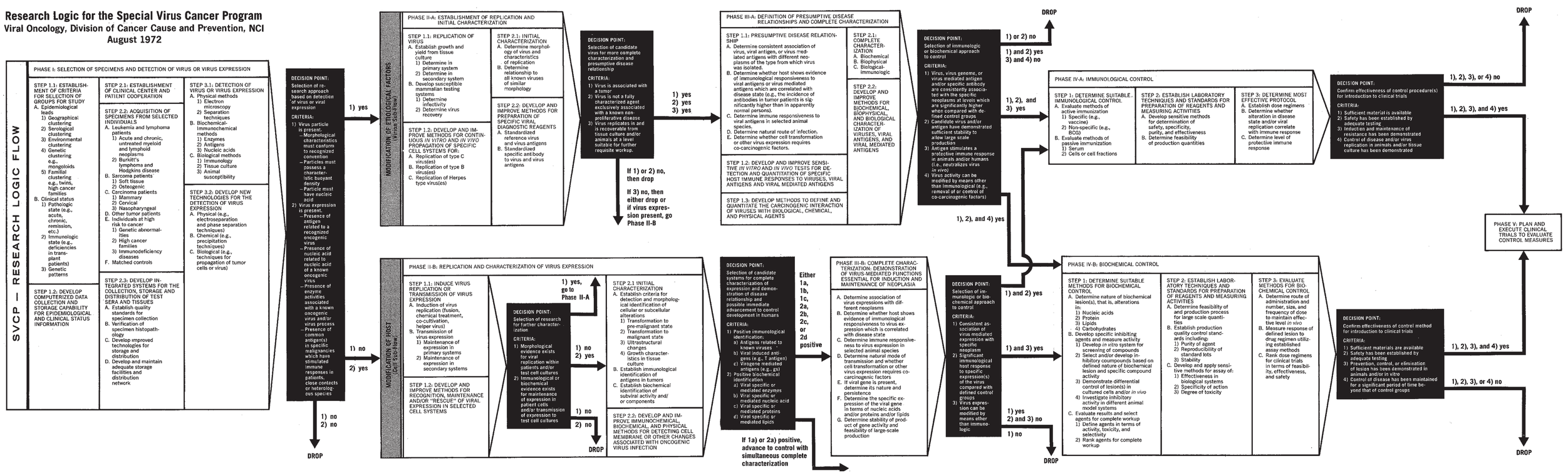
SVCP — RESEARCH LOGIC FLOW
PHASE I: SELECTION OF SPECIMENS AND DETECTION OF VIRUS OR VIRUS EXPRESSION
STEP 1.1: ESTABLISHMENT OF CRITERIA FOR SELECTION OF GROUPS FOR STUDY
A. Epidemiological leads
1) Geographical clustering
2) Serological clustering
3) Environmental clustering
4) Genetic clustering e.g., mongoloids
5) Familial clustering e.g., twins, high cancer families
B. Clinical status
1) Pathologic state (e.g., acute, chronic, remission, etc.)
2) Immunologic state (e.g., deficiencies in transplant patients)
3) Genetic patterns
STEP 1.2: DEVELOP COMPUTERIZED DATA COLLECTION AND STORAGE CAPABILITY FOR EPIDEMIOLOGICAL AND CLINICAL STATUS INFORMATION
STEP 2.1: ESTABLISHMENT OF CLINICAL CENTER AND PATIENT COOPERATION
STEP 2.2: ACQUISITION OF SPECIMENS FROM SELECTED INDIVIDUALS
A. Leukemia and lymphoma patients
1) Acute and chronic, untreated myeloid and lymphoid neoplasms
2) Burkitt's lymphoma and Hodgkins disease
B. Sarcoma patients
1) Soft tissue
2) Osteogenic
C. Carcinoma patients
1) Mammary
2) Cervical
3) Nasopharyngeal
D. Other tumor patients
E. Individuals at high risk to cancer
1) Genetic abnormalities
2) High cancer families
3) Immunodeficiency diseases
F. Matched controls
STEP 2.3: DEVELOP INTEGRATED SYSTEMS FOR THE COLLECTION, STORAGE AND DISTRIBUTION OF TEST SERA AND TISSUES
A. Establish quality standards for specimen collection
B. Verification of specimen histopathology
C. Develop improved technologies for storage and distribution
D. Develop and maintain adequate storage facilities and distribution network
STEP 3.1: DETECTION OF VIRUS OR VIRUS EXPRESSION
A. Physical methods
1) Electron microscopy
2) Separation techniques
B. Biochemical-immunochemical methods
1) Enzymes
2) Antigens
3) Nucleic acids
C. Biological methods
1) Immunology
2) Tissue culture
3) Animal susceptibility
STEP 3.2: DEVELOP NEW TECHNOLOGIES FOR THE DETECTION OF VIRUS EXPRESSION
A. Physical (e.g., electroseparation and phase separation techniques)
B. Chemical (e.g., precipitation techniques)
C. Biological (e.g., techniques for propagation of tumor cells or virus)
DECISION POINT:
Selection of research approach based on detection of virus or viral expression
CRITERIA:
1) Virus particle is present:
– Morphological characteristics must conform to recognized convention
– Particles must possess a characteristic buoyant density
– Particle must have nucleic acid
2) Viral expression is present.
– Presence of antigen related to a recognized oncogenic virus
– Presence of nucleic acid related to nucleic acid of a known oncogenic virus
– Presence of enzyme activities associated with a known oncogenic virus and/or virus process
– Presence of common antigen(s) in specific malignancies which have stimulated immune responses in patients, close contacts or heterologous species
1) yes
1) no
2) yes
2) no
DROP
MODIFICATION OF ETIOLOGICAL FACTORS (Virion Sub-Flow)
PHASE II-A: ESTABLISHMENT OF REPLICATION AND INITIAL CHARACTERIZATION
STEP 1.1: REPLICATION OF VIRUS
A. Establish growth and yield from tissue culture
1) Determine in primary system
2) Determine in secondary system
B. Develop susceptible mammalian testing systems
1) Determine infectivity
2) Determine virus recovery
STEP 1.2: DEVELOP AND IMPROVE METHODS FOR CONTINUOUS *IN VITRO* AND *IN VIVO* PROPAGATION OF SPECIFIC CELL SYSTEMS FOR:
A. Replication of type C virus(es)
B. Replication of type B virus(es)
C. Replication of Herpes type virus(es)
STEP 2.1: INITIAL CHARACTERIZATION
A. Determine morphology of virus and characteristics of replication
B. Determine relationship to all known viruses of similar morphology
STEP 2.2: DEVELOP AND IMPROVE METHODS FOR PREPARATION OF SPECIFIC VIRAL DIAGNOSTIC REAGENTS
A. Standardized reference virus and virus antigens
B. Standardized specific antibody to virus and virus antigens
DECISION POINT:
Selection of candidate virus for more complete characterization and presumptive disease relationship
CRITERIA:
1) Virus is associated with a tumor
2) Virus is not a fully characterized agent exclusively associated with a known neoproliferative disease
3) Virus replicates in and is recoverable from tissue culture and/or animals at a level suitable for further requisite workup.
1) yes
2) yes
3) yes
If 1) or 2) no, then drop
If 3) no, then either drop or if virus expression present, go Phase II-B
PHASE III-A: DEFINITION OF PRESUMPTIVE DISEASE RELATIONSHIPS AND COMPLETE CHARACTERIZATION
STEP 1.1: PRESUMPTIVE DISEASE RELATIONSHIP
A. Determine consistent association of virus, viral antigen, or virus mediated antigens with different neoplasms of the type from which virus was isolated.
B. Determine whether host shows evidence of immunological responsiveness to viral antigens or virus mediated antigens which are correlated with disease state (e.g., the incidence of antibodies in tumor patients is significantly higher than in apparently normal persons).
C. Determine immune responsiveness to viral antigens in selected animal species.
D. Determine natural route of infection.
E. Determine whether cell transformation or other virus expression requires co-carcinogenic factors.
STEP 1.2: DEVELOP AND IMPROVE SENSITIVE *IN VITRO* AND *IN VIVO* TESTS FOR DETECTION AND QUANTITATION OF SPECIFIC HOST IMMUNE RESPONSES TO VIRUSES, VIRAL ANTIGENS AND VIRAL MEDIATED ANTIGENS
STEP 1.3: DEVELOP METHODS TO DEFINE AND QUANTITATE THE CARCINOGENIC INTERACTION OF VIRUSES WITH BIOLOGICAL, CHEMICAL, AND PHYSICAL AGENTS
STEP 2.1: COMPLETE CHARACTERIZATION
A. Biochemical
B. Biophysical
C. Biological-immunologic
STEP 2.2: DEVELOP AND IMPROVE METHODS FOR BIOCHEMICAL, BIOPHYSICAL, AND BIOLOGICAL CHARACTERIZATION OF VIRUSES, VIRAL ANTIGENS, AND VIRAL MEDIATED ANTIGENS
DECISION POINT:
Selection of immunologic or biochemical approach to control
CRITERIA:
1) Virus, virus genome, or virus mediated antigen and/or specific antibody are consistently associated with the specific neoplasms at levels which are significantly higher when compared with defined control groups
2) Candidate virus and/or antigen have demonstrated sufficient stability to allow large scale production
3) Antigen stimulates a protective immune response in animals and/or humans (i.e., neutralizes virus *in vivo*)
4) Virus activity can be modified by means other than immunological (e.g., removal of or control of co-carcinogenic factors)
1) or 2) no
1) and 2) yes
3) and 4) no
DROP
1), 2), and 3) yes
1), 2), and 4) yes
PHASE IV-A: IMMUNOLOGICAL CONTROL
STEP 1: DETERMINE SUITABLE IMMUNOLOGICAL CONTROL
A. Evaluate methods of active immunization
1) Specific (e.g., vaccine)
2) Non-specific (e.g., BCG)
B. Evaluate methods of passive immunization
1) Serum
2) Cells or cell fractions
STEP 2: ESTABLISH LABORATORY TECHNIQUES AND STANDARDS FOR PREPARATION OF REAGENTS AND MEASURING ACTIVITIES
A. Develop sensitive methods for determination of safety, specificity, purity, and effectiveness
B. Determine feasibility of production quantities
STEP 3: DETERMINE MOST EFFECTIVE PROTOCOL
A. Establish dose regimens
B. Determine whether alteration in disease state and/or viral replication correlate with immune response
C. Determine level of protective immune response
DECISION POINT:
Confirm effectiveness of control procedure(s) for introduction to clinical trials
CRITERIA:
1) Sufficient material is available
2) Safety has been established by adequate testing
3) Induction and maintenance of resistance has been demonstrated
4) Control of disease and/or viral replication in animals and/or tissue culture has been demonstrated
1), 2), 3), or 4) no
1), 2), 3), and 4) yes
DROP
PHASE V: PLAN AND EXECUTE CLINICAL TRIALS TO EVALUATE CONTROL MEASURES
MODIFICATION OF HOST (Cell Sub-Flow)
PHASE II-B: REPLICATION AND CHARACTERIZATION OF VIRUS EXPRESSION
STEP 1.1: INDUCE VIRUS REPLICATION OR TRANSMISSION OF VIRUS EXPRESSION
A. Induction of virus replication (fusion, chemical treatment, co-cultivation, helper virus)
B. Transmission of virus expression
1) Maintenance of expression in primary systems
2) Maintenance of expression in secondary systems
STEP 1.2: DEVELOP AND IMPROVE METHODS FOR RECOGNITION, MAINTENANCE AND/OR "RESCUE" OF VIRAL EXPRESSION IN SELECTED CELL SYSTEMS
DECISION POINT:
Selection of research for further characterization
CRITERIA:
1) Morphological evidence exists for viral replication within patients and/or test cell cultures
2) Immunological or biochemical evidence exists for maintenance of expression in patient cells and/or transmission of expression to test cell cultures
1) yes, go to Phase II-A
1) no
2) yes
1) no
2) no
DROP
STEP 2.1 INITIAL CHARACTERIZATION
A. Establish criteria for detection and morphological identification of cellular or subcellular alterations
1) Transformation to pre-malignant state
2) Transformation to malignant state
3) Ultrastructural changes
4) Growth characteristics in tissue culture
B. Establish immunological identification of antigens in tumors
C. Establish biochemical identification of subviral activity and/or components
STEP 2.2: DEVELOP AND IMPROVE IMMUNOCHEMICAL, BIOCHEMICAL, AND PHYSICAL METHODS FOR DETECTING CELL MEMBRANE OR OTHER CHANGES ASSOCIATED WITH ONCOGENIC VIRUS INFECTION
DECISION POINT:
Selection of candidate systems for complete characterization of expression and demonstration of disease relationship and possible immediate advancement to control development in humans
CRITERIA:
1) Positive immunological identification:
a) Antigens related to known viruses
b) Viral induced antigens (e.g., T antigen)
c) Virogene-mediated antigens (e.g., gp)
2) Positive biochemical identification
a) Viral specific or mediated enzymes
b) Viral specific or mediated nucleic acid
c) Viral specific or mediated proteins
d) Viral specific or mediated lipids
Either 1a, 1b, 1c, 2a, 2b, 2c, or 2d positive
If 1a) or 2a) positive, advance to control with simultaneous complete characterization
PHASE III-B: COMPLETE CHARACTERIZATION: DEMONSTRATION OF VIRUS-MEDIATED FUNCTIONS ESSENTIAL FOR INDUCTION AND MAINTENANCE OF NEOPLASIA
A. Determine association of virus expressions with different neoplasms
B. Determine whether host shows evidence of immunological responsiveness to virus expression which is correlated with disease state
C. Determine immune responsiveness to virus expression in selected animal species
D. Determine natural mode of transmission and whether cell transformation or other virus expression requires co-carcinogenic factors
E. If viral gene is present, determine its nature and persistence
F. Determine the specific expression of the viral gene in terms of nucleic acids and/or proteins and/or lipids
G. Determine stability of product of gene activity and feasibility of large-scale production
DECISION POINT:
Selection of immunologic or biochemical approach to control
CRITERIA:
1) Consistent association of virus mediated expression with specific neoplasm
2) Significant immunological host response to specific expression(s) of the virus compared with defined control groups
3) Virus expression can be modified by means other than immunologic
1) and 2) yes
1) and 3) yes
1) yes
2) and 3) no
1) no
DROP
PHASE IV-B: BIOCHEMICAL CONTROL
STEP 1: DETERMINE SUITABLE METHODS FOR BIOCHEMICAL CONTROL
A. Determine nature of biochemical lesion(s), that is, alterations in:
1) Nucleic acids
2) Protein
3) Lipids
4) Carbohydrates
B. Develop specific inhibiting agents and measure activity
1) Develop *in vitro* system for screening of compounds
2) Select and/or develop inhibitory compounds based on defined nature of biochemical lesion and specific compound activity
3) Demonstrate differential control of lesion(s) in cultured cells and/or *in vivo*
4) Investigate inhibitory activity in different animal model systems
C. Evaluate results and select agents for complete workup
1) Define agents in terms of activity, toxicity, and selectivity
2) Rank agents for complete workup
STEP 2: ESTABLISH LABORATORY TECHNIQUES AND STANDARDS FOR PREPARATION OF REAGENTS AND MEASURING ACTIVITIES
A. Determine feasibility of and production process for large scale quantities
B. Establish production quality control standards including:
1) Purity of agent
2) Reproducibility of standard lots
3) Stability
C. Develop and apply sensitive methods for assay of:
1) Effectiveness in biological systems
2) Specificity of action
3) Degree of toxicity
STEP 3: EVALUATE METHODS FOR BIOCHEMICAL CONTROL
A. Determine route of administration and number, size, and frequency of dose to maintain effective level *in vivo*
B. Measure response of defined lesion to drug regimen utilizing established assay methods
C. Rank dose regimens for clinical trials in terms of feasibility, effectiveness, and safety
DECISION POINT:
Confirm effectiveness of control method for introduction to clinical trials
CRITERIA:
1) Sufficient materials are available
2) Safety has been established by adequate testing
3) Prevention, control, or elimination of lesion has been demonstrated in animals and/or in vitro
4) Control of disease has been maintained for a significant period of time beyond that of control groups
1), 2), 3), and 4) yes
1), 2), 3), or 4) no
DROP